Remarks

Summary of the August 25, 2009 Interview

Applicant arranged for an interview with the Examiner to point out the Lohning et al. PCT/EP00/06968 (WO2001/05950) publication of January 25, 2001. During the interview, the Amendment and Request for consideration filed by applicant on September 26, 2008 was discussed, as was the fact that applicant overlooked the related PCT publication.

Claims

Claims 1-19 are pending. The above amendments are made solely for the purposes of clarification.

Response to §103(a) Rejection in the Office Action mailed June 26, 2008

In the office action mailed on June 26, 2008, the Examiner rejected claims 1-19 under U.S.C. 103(a) as obvious over Lohning et al. (US 2002/0034733) in view of Burger et al. (Appl. Microbiol. Biotechnol. (1999) 52:345-353). In the above mentioned interview, applicant pointed out the PCT publication of PCT/EP00/06968 (WO2001/05950) on January 25, 2001. Applicant, therefore, provides the following remarks in response to the previous U.S.C. 103(a) rejection, as if the PCT publication of PCT/EP00/06968 (WO2001/05950) on January 25, 2001 were cited in view of Burger et al. (Appl. Microbiol. Biotechnol. (1999) 52:345-353).

The Examiner asserts that Lohning et al. discloses phagemid vectors comprising a prokaryotic promoter, a first nucleic acid sequence encoding an immunoglobulin-presenting polypeptide, a second nucleic acid encoding a first Ig polypeptide and a third nucleic acid encoding a second Ig polypeptide, wherein a first and second associating agent are fused to or comprised within said Ig-presenting polypeptide and the first Ig polypeptide and comprise a cysteine residue, wherein the first and second Ig polypeptide self-associate to form Fabs.

The Examiner states, however, that Lohning et al. does not disclose the single, tricistronic vector of the claimed invention. The Examiner asserts that Burger et al. makes up for this deficiency by teaching tricistronic vectors to achieve stable expression of three polypeptides of interest, two of which are Ig polypeptides. The Examiner states that the tricistronic vector of Burger et al. is useful for industrial scale production.

In order to present a prima facie case of non-obviousness, the Examiner must articulate one of the KSR v. Teleflex rationales outlined in MPEP 2143, or find that the teaching-suggestion-motivation ("TSM") test outlined in MPEP 2143.01 is satisfied, or find

that a reasonable expectation of success existed to combine the prior art under MPEP 2143.02. Here, the Examiner argues that it would be obvious to use the vectors described by Burger et al. to express the genes of Lohning et al. because both are concerned with the expression of three different gene products. The Examiner also argues that Burger et al. provides the motivation to use tricistronic vectors in phage display because of the usefulness of Burger et al.'s vectors for obtaining stable expression of three gene products. Applicant respectfully traverses.

Lohning et al. fails to describe tricistronic vectors. Burger et al. describes the use of tricistronic vectors, but the combination of Burger et al. with Lohning et al. fails to teach or suggest the instantly claimed invention for the following reasons: 1) Burger et al.'s difficulties in predictably expressing only two structural proteins would not have provided the motivation or expectation of success for a person of ordinary skill in the art to attempt the expression of three structural polypeptides; and 2) Burger et al.'s used the tricistronic vector for a completely different purpose than the present application, the creation of a cell line for large scale production, which provides no motivation or expectation of success for the present claimed invention.

1) Burger et al.'s difficulties in predictably expressing two structural proteins provided no motivation or expectation of success to attempt the expression of three structural polypeptides.

Lohning et al. dealt with the expression of three structural polypeptides by using a dual vector system. The dual vector system was used because of the perceived difficulties of expressing multiple polypeptides from one vector. At the time it was thought that a single vector would be overloaded, especially with the use of one promoter, and not provide satisfactory yields. The problem with the dual vector system, however, is that it requires a selection protocol to verify that the phage or phagemid, for example, contain both vectors. It is essentially impossible, however, to use a selection protocol for phage display because of the large scale of the library, which includes $\sim 10^{10}$ phages. In addition, two vectors can be incompatible, which can hinder expression. A dual vector system provided less than desirable display rates, as shown in Tables I and II of the present application. Therefore, a new vector system was needed. Despite the expectation that the above problems would cause a tricistronic vector to provide even lower display rates than the dual vector system (utilizing a dicistronic vector), the use of the tricistronic vector showed unexpectedly high display rates, as shown in Table II. As a result the present application teaches the use of the tricistronic vector in, for example, phage display.

The Examiner states that Burger et al. would have motivated a person of skill in the art to use tricistronic vectors because of Burger et al.'s stable expression of three gene products. Burger et al., however, had great difficulties using a tricistronic vector to predictably express *two* structural polypeptides; accordingly, Burger et al.would not have motivated a person of ordinary skill in the art to use the same vectors to attempt to express three structural polypeptides that must associate upon expression. Because of the difficulties shown in Burger et al., a person of skill in the art would likely conclude that the tricistronic vector would not be useful to express three structural gene products.

The expression products in Burger et al. differ from that of the claimed invention, as Burger et al.'s vector led to the expression of only two structural polypeptides, the Ig light chain and Ig heavy chain fusion polypeptide, and puromycin acetyltranferase (pac), which acts as a selection vehicle. In the article, Burger et al. highlighted the problems associated with tricistronic vectors as Southern blot analysis showed an extremely variable mRNA copy number (page 348, column 1) and the tricistronic transfectants produced truncated RNA and unusually high molecular weight mRNA (page 348, column 2). In addition, multiple clones, 1-8, 3-1, and 3-3 failed to reveal any protein equivalent to the heavy chain Ig (page 348, column 2). Burger et al.found that only one tricistronic clone was notably productive, clone 3-2 (page 348, column 2). As a result, transfection had to be repeated to produce viable clones (page 348, column 2). The results show that Burger et al. had great difficulty in creating clones that predictably expressed the desired two gene products. These results would not have motivated a person of skill in the art nor provided a reasonable expectation of success to use tricistronic vectors to express three structural polypeptides as in the currently claimed invention, where the three structural polypeptides are an Ig-presenting polypeptide, for example, a phage coat protein, a first and a second Ig polypeptide.

In addition, phage display, for example, differs from the production of cell lines in Burger et al. In routine phage display, the phage are not evaluated for successful expression and no selection vehicle can be used; therefore, a greater predictability of reliable expression is needed than that provided by Burger et al. Burger et al.'s methods provide the ability to evaluate each individual cell line after transfection for its level of expression and to complete multiple transfections as necessary. Since phage display does not provide for either of these quality assurance steps, Burger et al.'s low level of predictability would not motivate the use of tricistronic vectors in, for example, phage display.

In addition, the present claims differ from the application in Burger et al. in that the three structural polypeptides, the Ig-presenting polypeptide, and first and a second Ig

polypeptide, must then self-associate in order to display functional Ig polypeptides. Burger et al. was not concerned with the self-association of the expression products as the heavy and the light chains were extracted from the cells as supernatant, and their association could be accomplished at a later time. Therefore, no motivation or reasonable expectation of success was shown by Burger et al. that three structural polypeptides could be reliably expressed and subsequently self-asssociate.

2) Burger et al.'s use of the tricistronic vector for a completely different purpose than the present application provides no motivation or expectation of success.

Burger et al. used a tricistronic vector for a completely different purpose than the present application. Burger et al.'s goal was the production of a high yield, stable cell line. Burger et al. was concerned with the amount of expression, and showed that with trial and error a cell line could be created that provided a high level of expression of the two structural polypeptides.

Phage display, for example, has a completely different goal. In phage display utilizing gIII, only a handful of Ig polypeptides are displayed per phage; accordingly, high expression is not the goal. Phage display requires a balanced and equal expression of each of the three structural polypeptides, so that fully functional Ig polypeptides are displayed. In an embodiment of the present disclosure, the vector uses an inducible promoter providing for a limited amount of expression within the phage. Higher expression is not the goal, and in fact, could lead to the greater expression and display of non-functional dimers that could prevent the successful display of functional Ig polypeptides.

Burger's completely different application with differing goals would not have provided the motivation or a reasonable expectation of success for the use of tricistronic vectors in phage display.

IDS

An IDS was filed on April 6, 2009. Applicants respectfully request that each listed document be considered by the Examiner and be made of record in the present application and that an initialed copy of Form PTO/SB/08 be returned in accordance with MPEP §609.

Priority

Currently, PAIR does not identify the priority claim to U.S. application serial number 60/399,150 filed on July 30, 2002. This priority was properly claimed, however, in the Application Date Sheet filed upon national stage entry on January 27, 2005. Both the Notice

of DO/EO Missing Requirements Mailed on August 19, 2005 and the US patent application publication number 20060121563 A1 show the above priority claim. Applicant respectfully requests that PAIR be updated to include the priority claim to U.S. application serial number 60/399,150 filed on July 30, 2002.

CONCLUSION

In view of the foregoing arguments, Applicants respectfully submit that the application is in condition for allowance. Should the Examiner feel that there are any issues outstanding after consideration of this response, the Examiner is invited to contact the undersigned to expedite prosecution of the application.

The Commissioner is hereby authorized by this paper to charge any fees during the entire pendency of this application including fees due under 37 C.F.R. §§1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account 50-4520. **This paragraph is intended to be a CONSTRUCTIVE PETITION FOR EXTENSION OF TIME in accordance with 37 C.F.R. §1.136(a)(3).**

Respectfully submitted,

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